THE COMBINED EFFECT OF CYCLOPROPANE AND THE DEPOLARIZERS ON ISOLATED HUMAN MUSCLE

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IN a previous study, it was shown that cyclopropane exerts a positive inotropic action on skeletal muscle, resulting in a marked increase in the tension developed by contractions evoked by both direct and indirect stimulation.[1] It was also shown that in the presence of a small amount of *d*-tubocurarine, cyclopropane increased the neuromuscular block produced by the *d*-tubocurarine but still produced an increase in the strength of the direct response. These observations led us to assume that the sites of action of cyclopropane were distributed over the whole muscle membrane. With this assumption in mind, the following study was undertaken to answer the question as to how the positive inotropic action of cyclopropane would be modified by the addition of suitable amounts of the depolarizing relaxants.

Received from the Department of Surgery, Division of Anesthesiology, University of California Medical Center, Los Angeles 24, California, and accepted for publication March 29, 1961.

METHODS

The test object used in these experiments was the isolated human intercostal nerve-muscle preparation. The dissection and pharmacologic use of this preparation has previously been described in detail.[2] The conditions of the experiments were kept as close as possible to those of the previous study on cyclopropane.[1] Since it was found that the positive inotropic action of cyclopropane is proportional to its concentration in the gas mixture, lower concentrations were used in the present study (average 10 per cent) than those employed in the previous study (25, 30 and 50 per cent). The lower concentration of cyclopropane still possesses a marked positive inotropic action, but avoids the technical difficulties presented by the higher concentrations, *e.g.*, strain gauge "pinning."

In all previous studies, the percentage block has been expressed as $I \times 100/D\text{-}A$,

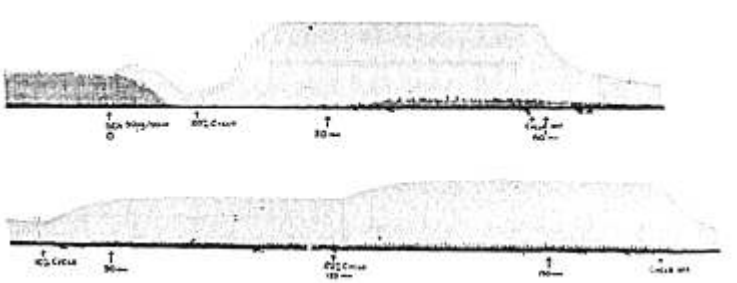

FIG. 1. Continuous record showing progression of neuromuscular block produced by succinylcholine chloride. Cyclopropane has been introduced into the gas mixture when the first phase block was at its maximum and again during the second phase. Note that, if the marked effect of cyclopropane on the direct response is ignored, the succinylcholine block of the indirect response appears to proceed without any significant alteration due to the addition of cyclopropane. Further discussion in text.

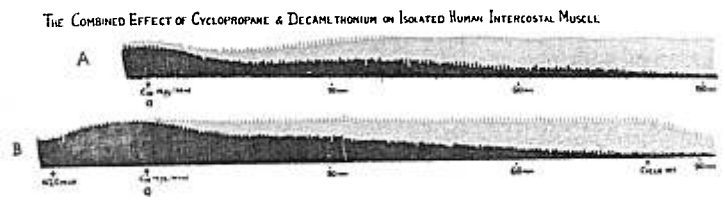

FIG. 2. *A*. Effect of 0.3 μg./ml. decamethonium bromide on isolated human intercostal muscle. To serve as control for: *B*. Same muscle as in figure 1*A*. Effect of same dose decamethonium added 15 minutes after 10 per cent cyclopropane was introduced into gas mixture. Drugs added as shown. Time marked in minutes after addition of decamethonium in both records. For discussion see text.

where D = height of direct response, I = height of indirect response and A = "apparent" block.[4] In the present study, however, the percentage block has been expressed as $I_2 \times 100/I_1$. Where I_1 = height of indirect response during control period, I_2 = height of indirect response at any given time after drug has been added. If used within the first 2 or 3 hours of the experiment, this expression is reasonably reliable since there is little decrement within this period.[4] It ignores the effect of cyclopropane on the direct response, but considers the effect of both drugs on the indirect response.[1] Direct response is the isometric contraction of the muscle fasciculus stimulated directly through its longitudinal axis by means of a 0.1 millisecond condenser discharge of supramaximal strength. Indirect response is the isometric contraction elicited by stimulating the motor nerve terminations and/or motor end-plate of the muscle fasciculus with a supramaximal 1–2.5 microsecond square wave stimulus with transversely placed electrodes at the area of maximal response.

RESULTS

Since the paralysis resulting from the addition of any "depolarizing" drug occurs in two

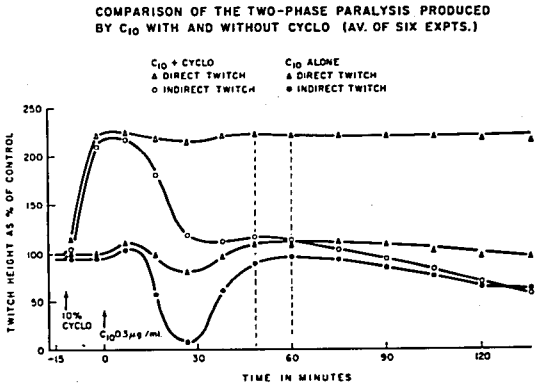

FIG. 3. Progression of neuromuscular block of decamethonium alone (closed circles and triangles) and of decamethonium in the presence of cyclopropane (open circles and triangles) plotted on arithmetic scale. Height of contractions at any given time expressed as percentage of control height as described under methods. Discussion in results.

phases, each differing from the other in many respects,[2] the experiments were divided into three groups as follows:

Experiments, 3 with succinylcholine and 3 with decamethonium (C-10), in which cyclopropane was introduced into the gas mixture while the muscle was in first phase paralysis and again when it had passed into the second phase. Figure 1 shows a typical record of contractions resulting from such an experiment. Note that gassing with 20 per cent cyclopropane has produced such a marked increase in the strength of the direct response that the strain gauge is unable to record the maximum tension developed; this was referred to above as strain gauge "pinning." Cyclopropane does not, however, seem to have affected the indirect response which progresses in the usual two phases of paralysis as described for depolarizing relaxants. The maximum recovery between the two phases appears about 10 to 15 minutes earlier in the presence of cyclopropane showing some antagonism between cyclopropane and the first phase of a depolarization block. The difference in recovery times can be seen

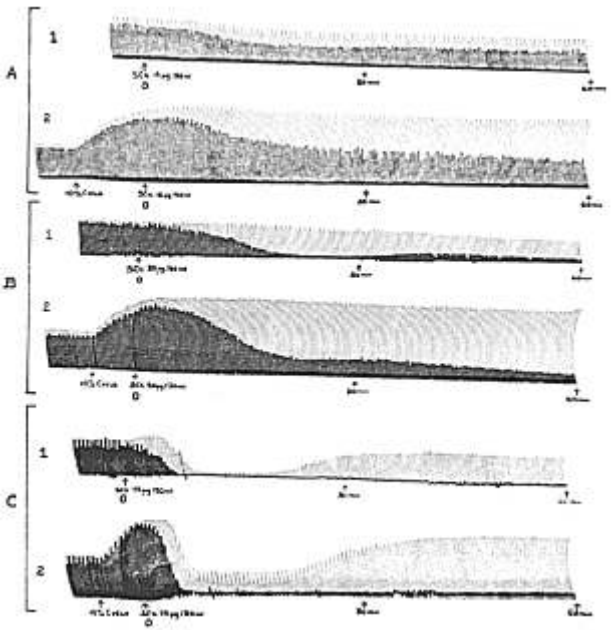

FIG. 4. First phase neuromuscular blocks produced by increasing doses of succinylcholine alone and in the presence of 10 per cent cyclopropane. Each record marked by the number 1 serves as a control for the corresponding record number 2. Note the first phase in figure *B* (2) is not as profound as in its control (fig. *B* (1)). This is due to the indirect response being at a higher level in the presence of cyclopropane. The regularly irregular direct response (alternately large and small) seen during the block in figure *C* (2) is due to the alternately changing polarity of the electrodes. It is seen sometimes in the absence of any drug (as in first part of figure *A* (1)).

by comparing the recovery times between the first phase blocks as graphed in figure 3. Recovery from the first block with C-10 alone occurs at approximately 50 minutes and with cyclopropane plus C-10 at 60 minutes.

Six experiments in which decamethonium bromide (C-10) 0.3 μg./ml., was administered after the cyclopropane had produced its maximum positive inotropic effect. This occurred in about 10 to 15 minutes.

Figure 2 shows records from such an experiment. Figure 2*A* is a record of contractions showing a two-phase block with C-10 0.3 μg./ml. When the second phase block was almost complete, the preparation was thoroughly washed with fresh saline and after a short control record (fig. 2*B*) 10 per cent cyclopropane was turned into the gassing circuit. When the direct and indirect response had reached their maximum height, C-10 was introduced into the bathing saline in the same dose as before. The subsequent paralysis could then be compared with that obtained with C-10 alone. It is difficult to draw any inference from the resulting record, especially during the first phase block, since during this period, the C-10 is overcoming the positive inotropic effect of the cyclopropane and, therefore, cannot be compared to the control. Note, however, that recovery from the first phase occurs about 10 minutes earlier in the presence of cyclopropane. If the percentage blocks at say 120 minutes are compared, no significant difference can be seen between the blocks produced by C-10 with or without cyclopropane.

To demonstrate this, the average heights of contractions obtained from the records of six experiments were plotted as twitch height against time (fig. 3). The twitch height at any time is shown on the ordinate as a percentage of the control, which was taken as 100 per cent.

In the third group of three experiments, different doses of succinylcholine were added to the bathing saline after 10 per cent cyclopropane had produced its maximum positive inotropic effect. The second phase of neuromuscular block proceeded in a manner similar to that described for the second group. First phase blocks are shown in figure 4. It appears that cyclopropane had antagonized the first phase, because maximum recovery between the two phases occurs slightly earlier in the presence of cyclopropane, even though the first phase block was most profound at about the same time in each case.

Discussion

These experiments on isolated human muscle fasciculus show that cyclopropane shortens the first phase of a depolarization paralysis but has no effect on the second phase block. The effect of cyclopropane on the direct response is not altered by the presence of moderate amounts of a depolarizing relaxant. We can perhaps assume that cyclopropane occupies receptor sites not occupied by a depolarizer during the second phase of paralysis.

It has been theorized that a second phase "depolarization" block is similar to that produced by curare.[2, 5] However, since cyclopropane increases the action of *d*-tubocurarine,[1] but does not affect the second phase of a depolarization block, there is a suspicion that *d*-tubocurarine occupies receptor sites other than those occupied by the depolarizers.

Summary

Experiments have been performed to demonstate the combined effect of cyclopropane and two "depolarizing" relaxants (decamethonium bromide and succinylcholine chloride) on isolated human intercostal nerve-muscle preparations.

From the results it is concluded that cyclopropane shortens the first phase but does not alter the end result of a two-phase depolarization paralysis of isolated nerve-muscle preparations. An incidental finding is that the neuromuscular block produced by *d*-tubocurarine and that produced by a depolarizer in its second phase behave quite differently in the presence of cyclopropane. Doubt is expressed whether there is any similarity between these two forms of paralysis.

Supported by U. S. Public Health Service Grant B-1203.

References

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RESERPINE Recovery curves of blood serotonin and pupil size in man after single large doses of reserpine are described. Reserpine induces a release of norepinephrine and serotonin from all tissues in which they are stored. These include the intestine, platelets, mast cells, adrenal medulla, spleen, aorta and brain. Five weeks must be allowed after the cessation of reserpine therapy in human beings for all drug effects to be considered absent. After a single large dose of reserpine, blood serotonin had returned to normal in five weeks and pupil size in seven days. The conclusion is that man is more sensitive than animals to the effects of reserpine. (*Freedman, D. X., and Benton, A. J.: Persisting Effect of Reserpine in Man, New Engl. J. Med. 264: 529 (Mar. 16) 1961.*)

RESPIRATORY UNIT A unit for the treatment of severe respiratory insufficiency was created at the Toronto General Hospital. In clinical charge of the unit is a team including an anesthetist, an otolaryngologist, a neurologist, and an internist. Specially trained nurses are essential. Respiration is maintained by intermittent positive pressure machines connected to cuffed orotracheal or tracheostomy tubes. This mode of therapy is used because it is applicable to any type of insufficiency, and permits easy nursing care, examination, and physiotherapy. The types of cases admitted are crushed chest, neurological disorders, barbiturate poisoning, postoperative respiratory failure, and chronic pulmonary disease with carbon dioxide narcosis. In many patients the primary condition is reversible, and the institution of adequate ventilation causes striking improvement and eventual return to normal life. (*Woolf, C.: Respiratory Unit at Toronto General Hospital, Canad. Med. Ass. J. 84: 466 (Mar. 4) 1961.*)

ENDOTRACHEAL CANNULAE Patients with permanent endotracheal respiration frequently show ulcerative lesions of the mucous membrane and tracheomalacia due to mechanical stimulation and irritation by silver. Polyvinyl cannulas are too easily deformed. All these difficulties are avoided by covering the endotracheal parts of silver cannulas with a plastic derivative of methacrylacid (Optodont). (*Rehm, H., Cädeke, R., and Böhm, R.: Technical Reference to Avoidance of Tracheal Lesions with Permanent Endotracheal Respiration, Der Anaesthesist 10: 55 (Feb.) 1961.*)

ASTHMA THERAPY A comparison was made of the effectiveness of the sublingual administration of nitroglycerine (0.6 mg.), erythrol tetranitrate (15 mg.) and isopropylarterenol (15 mg.) in the treatment of bronchial asthma. All agents proved to be effective in the symptomatic treatment of bronchial asthma but the potency and duration of the nitrites surpass that of isopropylarterenol. (*Hirshleifer, I., and Arora, Y.: Nitrites in Treatment of Bronchial Asthma, Dis. Chest 39: 275 (Mar.) 1961.*)